REMARKS/ARGUMENTS

In response to the Office Action of March 02, 2004, and telephonic interview conducted on October 21, 2004, Applicant requests re-examination and reconsideration of this application for patent pursuant to 35 U.S.C. 132.

Applicants would like to thank Examiner Nguyen for the courtesies extended during the telephonic interview conducted on October 21, 2004.

No new matter has been added by the amendments to the specification.

A second substitute Sequence Listing disclosing the originally filed sequence and other amendments corresponding to the second substitute Sequence Listing have been added.

The Prior Art section has been amended to correct a typographical error found in international application number and to include corresponding international publication number, on page 4, line 19.

No new matter has been added by amendments to claims.

So as to provide Examiner Nguyen an opportunity to fully consider all issues, Applicants are filing a Request for Continuing Examination concurrently herewith.

Claims 1, 36 and 41 have been amended. Claims 1, 36 to 43 are pending in the instant application.

Claims 1, 41 have been amended to clearly indicate the claims do not read on a naturally occurring protein, see page 31, lines 8-

11 for support.

Claim 36 has been amended to more clearly disclose the relationship between the mass spectrum profiles of an isolated biopolymer having SEQ ID NO.: 1 to mass spectrum profiles of peptides elucidated from said sample and confirming the presence of the isolated biopolymer marker having SEQ ID NO:1 in a sample that displays a peak profile at about 1077 Da in the mass spectrum. The above addition to the claims find basis throughout the originally filed disclosure, see for example page 17, lines 11 to 14 and page 27, lines 17 to 23.

Sequence Compliance

Applicants provided a Sequence Listing (in both paper and computer readable form) disclosing SEQ ID NO: 1 filed on April 19, 2002 and a substitute Sequence Listing on July 31, 2003. During the interview of October 21, 2004, Examiner Nguyen maintained the lack of support for the first and last amino acid residues of SEQ ID NO:1 as added by the substitute Sequence Listing field on July 31, 2003. Although Applicants contend that the first, Glu (E), and last, Gly (G), amino acids in SEQ ID NO: 1 were clearly shown in Figures 1 and 2 as originally filed, in order to further patent prosecution Applicants herein provide a second substitute Sequence Listing (in both paper and electronic computer readable form) to replace the previously submitted substitute Sequence Listing (filed on July 31, 2003). The second substitute Sequence Listing submitted herewith contains a Sequence Listing which removes the

first and last amino acid residues in SEQ ID NO: 1. The computer readable form of the second substitute Sequence Listing is identical to the paper copy of the second substitute Sequence Listing. The claims, as herein amended, limit the marker sequence to amino acid residues GDFLAEGGGVR as originally disclosed in the specification on page 27, line 18.

Specification

The amendment filed July 31, 2003 stands objected to under 35 U.S.C. 132 because it allegedly introduces new matter into the disclosure, specifically the alteration of SEQ ID NO: 1. The Examiner states that changes to page 19, lines 2 and lines 6 in the Brief Description of the Drawings section describing Figures 1 and 2 are improper.

Although Applicants contend the originally filed Figures 1 and 2 show the first (E) and last (G) amino acid residues of SEQ ID NO:1, were unintentionally not provided in the Sequence Listing ID dated April 19, 2002, Applicants have now removed the first (E) and last (G) amino acid residues of SEQ ID NO:1 and thus respectfully request that this objection under 35 U.S.C. 132, be withdrawn.

Rejection under 35 USC 101

Claim 1 stands rejected under 35 USC 101 as being directed to non-statutory subject matter. The Examiner states that the protein of claim 1 reads on a naturally occurring protein. As suggested by the Examiner, Applicants have amended claim 1 to include an "isolated" biopolymer marker thereby differentiating it from a

naturally occurring biopolymer. Thus, it is respectfully requested this rejection be withdrawn.

Rejection under 35 USC 112 (second paragraph)

Claims 36-40 stand rejected under 35 USC 112, second paragraph, as being indefinite for allegedly failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Examiner alleges that claims 36-40 are vague and indefinite with respect to the recitation in step c. It is allegedly unclear to the Examiner what criteria are used in comparing the mass spectrum profile of peptides isolated from the sample to the mass spectrum profile of a peptide having SEQ ID NO: 1. The Examiner questions does this mean 100% match? Is it the same to say that detection of SEQ ID NO: 1 in the patient sample is diagnostic for myocardial infarction? Additionally, the Examiner contends that the claims are confusing because it is unclear what "characteristics" are used as the basis of comparison. These characteristics are purportedly not clearly defined.

Claim 36 has been amended herein to remove the phrases "characteristic" and "diagnostic" and these limitations are not recited in any of the remaining pending claims.

Additionally, Applicants have amended the claims to clearly and concisely claim the presence of said isolated biopolymer marker having SEQ ID NO: 1 in the sample displaying a peak profile at about 1077 Da in the mass spectrum being indicative of a link to

myocardial infarction. This does not require 100% match or other characteristics for a basis of comparison, it simply requires a peak be present at about 1077 DA, which evidences a link to myocardial infarction. The instant specification fully supports the disease specific marker identified by the SEQ ID NO: 1, characterized as Alpha Fibrinogen, having a molecular weight of about 1077 daltons as set forth in Figure 2 being indicative of an individual suffering from myocardial infarction, see page 27, lines 17 to line 23.

Accordingly, Applicants have now clarified the metes and bounds of the claims and respectfully request that the above-discussed rejections under 35 USC 112 (second paragraph) be withdrawn.

Rejection under 35 USC 112 (first paragraph)

Claims 1 and 36-43 stand rejected under 35 U.S.C. 112, first paragraph, as allegedly failing to comply with the written description requirement. The claims allegedly contain subject matter not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors, at the time of the application, had possession of the claimed invention. The Examiner states the invention as currently amended is different from what is defined in the claim(s) and original specification because nothing in the specification leads one to predict that the peptide of SEQ ID NO: 1 comprises 13 amino acids with the first and last being Glu (E) and Gly (G), respectively.

As discussed above with respect to the objection to the specification, Applicants maintain that originally filed Figures 1 and 2 clearly disclose the first and last amino acid residues of SEQ ID NO: 1 as listed in Sequence Listing filed July 31, 2003, and thus, not new matter. However, in order expedite patent prosecution Applicants have now removed the first (E) and last (G) amino acid residues of SEQ ID NO:1 and thus respectfully request that this rejection be withdrawn.

Previously added claims 36-40 stand rejected as containing subject matter which was allegedly not described in such way as to reasonably convey to one skilled in the relevant art that the inventor(s) had possession of the claimed invention. Specifically, claims 36-40 recite a method for diagnosing myocardial infraction through the detection of a biopolymer marker from a patient sample and comparing the detected marker to the biopolymer marker having SEQ ID NO: 1. The Examiner alleges that while the specification does disclose how a biopolymer marker, identified as SEQ ID NO: 1, was identified from patient serum samples at pages 26 to 31, nowhere in the specification is there a teaching of detecting any other biopolymer marker and comparing the detected marker to SEQ ID NO. 1 and determining a disease state from the detected marker. The Examiner contends it is not clear what criteria are used in comparing the mass spectrum profile of the detected sample to the mass spectrum profile of SEQ ID NO 1. Additionally, during the interview conducted on October 21, 2004, the Examiner indicated

that there is no clear teaching in the specification, that after having detected SEQ ID NO. 1 in a sample, one may then definitively diagnose a patient as suffering from MI. The Examiner alleges that there is no disclosure in the specification regarding further testing of patients suspected of having MI, in which the claimed peptide is present, followed up or verified by a diagnosis of MI by other diagnostic methods.

Applicants respectfully disagree with the Examiner's above mentioned arguments, as claims 36 to 40 have been herein amended to clearly illustrate the comparison of a marker having SEQ ID NO:1 to mass spectrometric profile elucidated from a sample and then confirming, or verifying, the presence of the isolated biopolymer marker having SEQ ID NO:1 when the sample displays a peak profile at about 1077 DA, see for example page 12, lines 2-12. The criteria used in the comparison and subsequent confirmation of biopolymer having SEQ ID NO: 1 is the appearance of a peak at about 1077 DA in the mass spectrum of a sample, see page 27, lines 17-23.

In response to Examiner's argument regarding a teaching of detecting "other" biopolymer markers and comparing the detected markers to SEQ ID NO. 1 and determining a disease state from the detected marker. Applicants do not claim any other biopolymer markers; the claims, as pending, are drawn to determining the presence of a specific isolated biopolymer marker having SEQ ID NO:1 which is indicative of a link to a specific disease condition (myocardial infarction).

With respect to Examiner's argument that a separate confirmation diagnoses of a patient suffering from MI should be disclosed, Applicants point Examiner's attention to the instant specification on page 16, line 19 to page 17, line 6 which states subsequent to the isolation of particular disease state marker sequences as taught by the instant invention, the promulgation of various forms of risk-assessment tests are contemplated which will allow physicians to identify asymptomatic patients before they suffer an irreversible event such as diabetes, kidney failure, and heart failure, and enable effective disease management and preventative medicine. In other words, after identifying the mass spectrum peak profile of SEQ ID NO: 1 in a patient sample by the present method, the patient's disease is positively identified through other various risk-assessment tests.

Such routine risk-assessment tests generally include blood and urine analysis, x-rays, electrocardiogram (EKG), cardiac stress tests, computer assisted tomography (CAT) scans, magnetic resonance imagery (MRI), echocardiographic studies, Doppler analysis, angiograms, electromyograph (EMG), electroencephalograph (EEG) and the like, and are well known in the diagnostic art to assist physicians in forming a definitive diagnosis, see paragraph bridging page 1 and 2 in Applicant's co-pending application no. 09/846,330, now Pub. No. U.S. 2002/0160420, both applications were filed on April 30, 2001.

Thus, Applicants respectfully summit that the specification

does in fact teach that patients suspected of having MI, in which the claimed peptide was found to be present, were followed up or confirmed by a diagnosis of MI utilizing other routine diagnostic tests. However, the intended purpose of the invention is to provide improved, alternative means for diagnosis of MI which can easily be performed by an untrained individual without the need for additional testing. If "follow up" diagnostic methods are also required, then the diagnostic process is lengthened and the invention fails to fulfill its intended purpose.

Accordingly, Applicants have shown that they had possession of the invention, as defined by the claims as recited herein, at the time that the application was filed and thus respectfully request that this rejection be withdrawn.

Claims 36-40 also stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which is most nearly connected, to make and/or use the invention.

Claims 36-40 have been amended herein to clearly illustrate the comparison of a marker having SEQ ID NO:1 to a mass spectrometric profile elucidated from a sample and then confirming the presence of the isolated biopolymer marker having SEQ ID NO:1 when the sample displays a peak profile at about 1077 DA, such that the presence of the biopolymer is indicative of a link to MI.

Although Applicants believe that the instant specification fully supports the claim that an isolated peptide consisting of SEQ ID NO:1 is diagnostic for MI, in the interest of compact prosecution Applicants have amended the claim(s) to recite that the presence of the isolated biopolymer marker is indicative of a link to MI.

According to dictionary.com the term "linked" refers to the condition of being associated with or connected to (see attached). The instant specification fully supports a connection and/or an association of the claimed peptide with MI. The instant specification states on page 17, lines 11 to 14 as an objective of the instant invention the evaluation of samples containing a plurality of biopolymers for the presence of disease specific marker sequences which evidence a link to at least one specific disease state. The data presented in the figures further supports the association of the claimed peptide with MI.

The guidelines for a "test of enablement" indicate that if a statement of utility in the specification contains within it a connotation of how to use, 35 USC 112 is satisfied. Furthermore, it has been established that the mere fact that something has not previously been done clearly is not, in itself, a sufficient basis for rejecting all applications purporting to disclose how to do it. The instant application discloses a biopolymer marker having SEQ ID NO:1 which is linked to MI, such a marker has not previously been shown to be linked to MI. When a biopolymer marker is discovered to be associated with a disease state it carries with it a

connotation of potential diagnostics and/or therapeutics. Thus, based upon the statements made in the instant paragraph, the test for enablement is not sufficient to support an enablement rejection.

The skill in the art is high and it is obvious that no undue experimentation would be required for a skilled artisan to follow any of the protocols presented in the instant specification, since these protocol are well known in the art.

The Federal Circuit has repeatedly held that the "specification must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation'". Nevertheless, not everything necessary to practice the invention need be disclosed. In fact, what is well-known is best omitted. *In re Buchner*, 929 F.2d 660, 18 USPQ2d 1331, 1332 (Fe. Cir. 19991). What is conventional or well known to one of ordinary skill in the art not be disclosed in detail. See *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d at 1384, 231 USPQ at 94.(see MPEP 2164.01). A specification disclosure which contains a teaching of the manner and process of making an using an invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken in compliance with the enablement requirement of 35 USC 112, first paragraph, unless there is some reason to doubt the object truth of the statements contained therein which must be relied upon for enabling support. Assuming that sufficient reason for such doubt

exists, a rejection for failure to teach how to make and/or use will be proper on that basis. *In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971). See MPEP 2161.04.

The Examiner contends that a number of characteristics need to be considered in the development of any suitable diagnostic assay. These characteristics, upon which the Examiner appears to rely, are found in Strongin (1993, "Sensitivity, Specificity, and Predictive Value of Diagnostic Tests: Definitions and Clinical Applications", in Laboratory Diagnosis of Vial Infections, Lennette, e.,ed. Marcel Dekker, Inc. New York, pp. 211-219), which is allegedly relevant to the instant invention. The Strongin reference describes a set of statistical characteristics that a clinician can apply to confirm or exclude the diagnosis of disease. Each of the diagnostic procedures possesses a set of characteristics that determine how close the procedure in question compares to an "ideal" test, that is, one with 100% specificity and sensitivity, which as the text states is extremely uncommon.

The Examiner appears to believe that since the specification allegedly lacks any information regarding the patients from which the samples were taken, and whether any considerations were given to any of the statistical characteristics stated in the Strongin reference, it would require undue experimentation for one skilled in the art to make and use the invention as claimed.

Assuming *arguendo* that specific protocols were not included within the instant disclosure, Applicants do not agree that all

diagnostic tests must specifically disclose the maximum sensitivity desired, specificity desired and efficiency desired, and other statistical analysis, as set forth in the Strongin reference, in order to meet the enablement requirement. Moreover, the data in Figure 1 and herein attached Appendix A do, in fact, disclose information regarding the patients from which the samples were taken, i.e. gender, age, disease. Furthermore, the specification does disclose how the diagnostic tests were performed in the Background of the Invention section. This section discusses various prior art mass spectrometer formats for use in analyzing the translation products of the present invention, see page 2, line 13-page 4, line 4 and page 27, lines 10-16. The specification discloses that the mass of the target polypeptide determined by mass spectrometry is then compared to the mass of a reference polypeptide of known identity.

The Examiner asserts that the data presented in Figure 1 is not convincing, nor does it clearly demonstrate that SEQ ID NO:1 is indicative of myocardial infarction (MI).

In response to the Examiner's assertion, Applicants previously submitted a Declaration (and Figure) under 37 CFR 1.132, dated July 31, 2003. The figure attached to the declaration provides side-by-side profiles (obtained using techniques of mass spectrometry) of normal human sera versus sera from patients having a history of myocardial infarction. This profile comparison clearly evidences the absence of the 1077 Dalton marker (SEQ ID NO: 1) in normal

human sera and thus establishes the specificity of the 1077 Dalton peptide as a biopolymer marker which when present in the sera is diagnostic for myocardial infarction.

During the interview of October 21, 2004, and in the Response to Arguments Section of the instant Office Action, the Examiner questioned whether the number of patients in the study, e.g. 5 patients in FIGURE 1, are statistically significant to conclude myocardial infarction. In response, Applicants herein provide an additional Declaration under 37 CFR 1.132 with attached Appendix A. Appendix A was originally filed in Applicant's application no. **09/846,330,** PG Pub. No. U.S. 2002/0160420. This Appendix A does not represent results obtained from additional experimentation. This data was obtained in the original experiments performed at the time of the invention.

The data set illustrated in FIGURE 1 of the instant application can be found on page A1 of Appendix A at MW 1077. Appendix A illustrates data obtained from a study of over 500 patients suffering from a variety of disease states, e.g. stroke, CHF, insulin resistance, MI, etc. The data includes a patient history, disease and protein name, molecular weight and the identified peptide sequence associated with the disease. The specification of 09/846,330 literally states at page 32, lines 9 to 15;

> Appendix A clearly illustrates patient specific samples obtained and the data used to formulate a library of

proteomic materials having characteristics identifiable with both normal and abnormal physiological conditions or predictive hallmarks thereof. Data which is exemplary of the information retrieved via the novel proteomic investigative techniques of the instant invention are set forth in Appendix A.

Appendix A illustrates the link between the detected biopolymer of SEQ ID NO: 1 which is positively identified through the instant method and a particular disease state. The link between MI and the instant biopolymer is clearly shown even when fragments of the instant biopolymer peptide of SEQ ID NO. 1 are detected. For example, patient (# SJ CON 07) contains a fragment (DFLAEGGGVR) of the alpha fibrinogen protein, see row 1, from top on page A1. In patient (# SJ CON 06) the biopolymer marker having SEQ ID NO: 1 (GDFLAEGGGVR) was also positively identified and diagnosed with MI, see page A1 row 4, from top, thereby further evidencing the link between the presence of biopolymer having SEQ ID NO: 1 with an association to MI. The data obtained in Appendix A illustrates a statically significant number of patients with a variety of different diseases wherein SEQ ID NO. 1, or a fragment thereof, was confirmed and linked to MI.

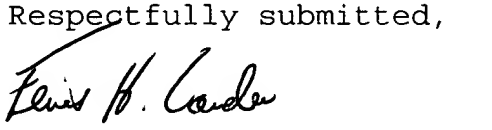
In conclusion, Applicants claim that the presence of SEQ ID NO:1 is indicative of a link to myocardial infarction; a statement which is enabled by the data presented in figure 1, Declaration filed July 31, 2003 and Appendix A. Applicants assert that one of

ordinary skill in the art when reviewing the instant specification and declaration filed herewith would recognize how to use the claimed peptide as a marker for myocardial infarction. Thus, Applicants respectfully request that this rejection under 35 U.S.C. 112, first paragraph now be withdrawn.

CONCLUSION

In light of the foregoing remarks, amendments to the specification and amendments to the claims, it is respectfully submitted that the Examiner will now find the claims of the application allowable. Favorable reconsideration of the application is courteously requested.

Respectfully submitted,



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